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TUBERCULOSIS MINISYMPOSIUM

Imaging recommendations and algorithms for pediatric tuberculosis: part 1—thoracic tuberculosis

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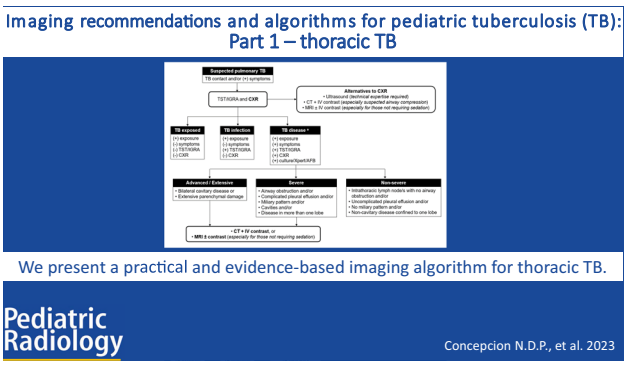
Abstract

Tuberculosis (TB) remains a global health problem and is the second leading cause of death from a single infectious agent, behind the novel coronavirus disease of 2019. Children are amongst the most vulnerable groups affected by TB, and imaging manifestations are different in children when compared to adults. TB primarily involves the lungs and mediastinal lymph nodes. Clinical history, physical examination, laboratory examinations and various medical imaging tools are combined to establish the diagnosis. Even though chest radiography is the accepted initial radiological imaging modality for the evaluation of children with TB, this paper, the first of two parts, aims to discuss the advantages and limitations of the various medical imaging modalities and to provide recommendations on which is most appropriate for the initial diagnosis and assessment of possible complications of pulmonary TB in children. Practical, evidence-based imaging algorithms are also presented.

Graphical Abstract



Keywords Chest · Children · Computed tomography · Pediatric · Pleura · Pulmonary · Radiograph · Tuberculosis

Introduction

Tuberculosis (TB) remains a global health concern, particularly in Asia, Africa, Latin America and Eastern Europe. Despite the advances in diagnosis and treatment protocol, the worldwide TB burden remains enormous. Tuberculosis was the leading cause of death from a single infectious agent until the emergence of the severe acute respiratory syndrome coronavirus 2 infection, coronavirus disease 2019 [1].

Children are amongst the most vulnerable groups because of their immature immune system and other related factors. Radiological manifestations of TB in children differ from those in adults, with pulmonary disease and lymphadenopathy being the most common thoracic TB manifestations in children. These

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abnormalities demonstrate a spectrum of both clinical and imaging manifestations.

Even with technological improvements in the armamentarium of medical imaging tools, chest radiography (CXR) is still the radiological standard in the initial evaluation of children with suspected TB. Medical imaging is also helpful in the assessment of acute and chronic complications, response to treatment, for image-guided intervention and in excluding other underlying pathologic processes. The purposes of this article are to (1) discuss the various imaging modalities utilized in the evaluation of suspected thoracic TB in children; (2) highlight the strengths and limitations of these imaging modalities in the diagnosis of pediatric thoracic TB; (3) review the spectrum of both clinical and imaging manifestations of thoracic TB; (4) provide a practical approach and recommendations for the diagnosis of thoracic TB in children through imaging; and (5) present an up-to-date evidence-based imaging algorithm that will serve as a guide for both radiologists and clinicians.

An extensive search of the medical literature, which included peer-reviewed systematic reviews and meta-analyses, review articles, evidence-based guidelines and consensus statements, was performed. All the available information was synthesized, considering the available clinical scenarios and spectrum of thoracic TB manifestations, as well as availability of resources (which affects the choice of imaging). The authors are well-published, practice in TB endemic areas and have an average of more than 21 years' experience (range from 16 years to 24 years). Most (S.A., N.D.P.C., B.F.L. and K.S.S.) are also members of the World Federation of Pediatric Imaging (WFPI) childhood tuberculosis group.

Pulmonary tuberculosis

Overview

Tuberculosis can affect virtually all organs of the body, but most commonly involves the thorax [2, 3]. Thoracic involvement in childhood TB is primarily nodal, pulmonary or a combination of these [4].

In children, diagnosis is usually epidemiological and indirect. Symptoms which are nonspecific include but are not limited to chronic cough, weight loss or failure to thrive, persistent unexplained fever and/or persistent unexplained lethargy or reduced activity. Childhood TB can be classically categorized as TB exposure, TB infection, possible or probable TB disease or confirmed TB disease depending on various factors: (1) presence of exposure, (2) reaction to the tuberculin skin test or interferon-gamma release assay, (3) presence or absence of symptoms, (4) imaging findings and/or (5) result of TB culture, Xpert *Mycobacterium tuberculosis*/rifampicin assay or acid-fast bacilli test if available [5]. Moreover, TB disease may be stratified into non-severe, severe and advanced/extensive disease, depending on symptomatology and imaging findings [6].

Imaging plays a major role in the diagnosis and follow-up (to assess treatment response and for detection of complications) in thoracic TB. In general, particularly in low-resource areas, the main diagnostic imaging tools are CXR and/or ultrasound (US) where available, while computed tomography (CT) and magnetic resonance imaging (MRI) which are mainly available in high-resource areas or tertiary centers are very costly and reserved for complicated cases [4, 5, 7, 8].

Imaging modalities

Chest radiography

The CXR remains an important imaging tool for patients suspected to have pulmonary TB [4, 5, 9–12]. It is however insensitive and nonspecific for TB and has poor interobserver agreement [5, 10, 13–19]. Up to 15% of patients with confirmed TB may have normal CXR findings [4, 5, 20–22]. The use of CXR as a screening tool in pediatric TB contacts is strongly supported, except for completely asymptomatic subjects in low-resource settings. Although the frequency of abnormal CXR findings that are consistent with TB amongst asymptomatic pediatric contacts is very low [23], some recent studies show that radiographic findings inconsistent with TB in these children may indicate beginning or subclinical disease [24, 25]. Pulmonary TB has been shown to be more common ($P < 0.05$) in children with co-morbidities than in those without [26].

Regional (hilar or mediastinal) lymphadenopathy is the radiological hallmark (but not pathognomonic) of primary TB disease in childhood [4, 5, 11, 13, 16, 27–30], with or without lung parenchymal opacities [11, 30]. Lymphadenopathy can be visualized in 50% to 70% of cases from 1–3 months after exposure [5, 8], and decreases with increasing age [13, 14]. The prevalence of lymphadenopathy approaches 100% in children below 3 years of age but is lower (88%) in older children. In contrast, the prevalence of parenchymal involvement is lower in children less than 3 years of age (51%) and significantly higher (78%) in older children [5, 28]. However, it is difficult to identify with certainty the presence of enlarged lymph nodes on CXR [5, 19, 31–33], because lymphadenopathy in young children can be obscured by vascular and other mediastinal structures and particularly by a large thymus [10, 12, 19, 31, 33].

In children with inadequate immunity, the primary disease can progress contiguously or hematogenously [5, 34]. Contiguous progression of disease is seen as homogeneous parenchymal consolidation and lymphadenopathy.

Compression of an airway by adjacent enlarged nodes results in overinflation (if partial obstruction) or atelectasis (if complete obstruction) because of smaller and more pliable airways in children [5, 11, 13, 14, 30, 35, 36]. The most reliable radiographic feature of lymphadenopathy is airway compression [13, 37] (Fig. 1). This lymphobronchial involvement/airway compression is strongly associated with confirmed pulmonary TB, significantly more frequently observed in infants compared to older children, although limited again by poor interobserver agreement [11, 12, 31, 33, 38]. Further imaging with cross-sectional modalities is thus recommended.

Hematogenously disseminated infection is termed "miliary TB" and presents with innumerable ≤ 2 mm non-calcified nodules diffusely scattered throughout both lungs [5, 8, 32, 35, 39, 40]. This nodular pattern, although not 100% specific, is commonly seen in TB [5, 40]. However, the miliary pattern can be easily missed on the CXR in up to 50% of cases [41, 42] and CXR is initially normal in 25% to 40% of cases [5, 8, 13, 32–43].

Pleural involvement is a common complication of thoracic TB and its prevalence increases with age. Pleural effusions can be associated with air-space consolidation and may be bilateral or loculated [5].

Congenital TB is an extremely rare *Mycobacterium tuberculosis* infection transmitted from the mother to the fetus [44] with only 300–400 reported cases [45, 46]. Chest radiographs may be normal initially [44–48]. The most common reported findings which may appear after 4–8 weeks are miliary pattern, multiple pulmonary nodules, lobar pneumonia and rarely, bronchopneumonia, interstitial pneumonia and mediastinal lymphadenopathy [45, 46, 48]. Ultrasound may show hypoechoic foci in the liver or spleen, ascites and abdominal lymphadenopathy. CT and MRI, if available, may be useful for unconfirmed or complicated cases [8, 46].

A CXR provides supportive evidence for diagnosing a patient suspected to have extra-pulmonary TB; e.g., 20% to 60% of children with abdominal TB have pulmonary disease [49, 50].

Ultrasound

Ultrasonography has many advantages over other imaging modalities, namely, (1) no ionizing radiation, (2) no sedation needed, (3) more cost-effective than cross-sectional imaging, and (4) can be portable. Because of these, US is becoming universally available even in low-resource areas [4, 10, 16, 51].

Ultrasound is primarily used in the evaluation of pleural fluid, but recent technological advancements have also improved the spatial resolution, tissue penetration and characterization of the peripheral lung parenchyma, and US may be useful for the detection of mediastinal lymphadenopathy [14, 51–56].

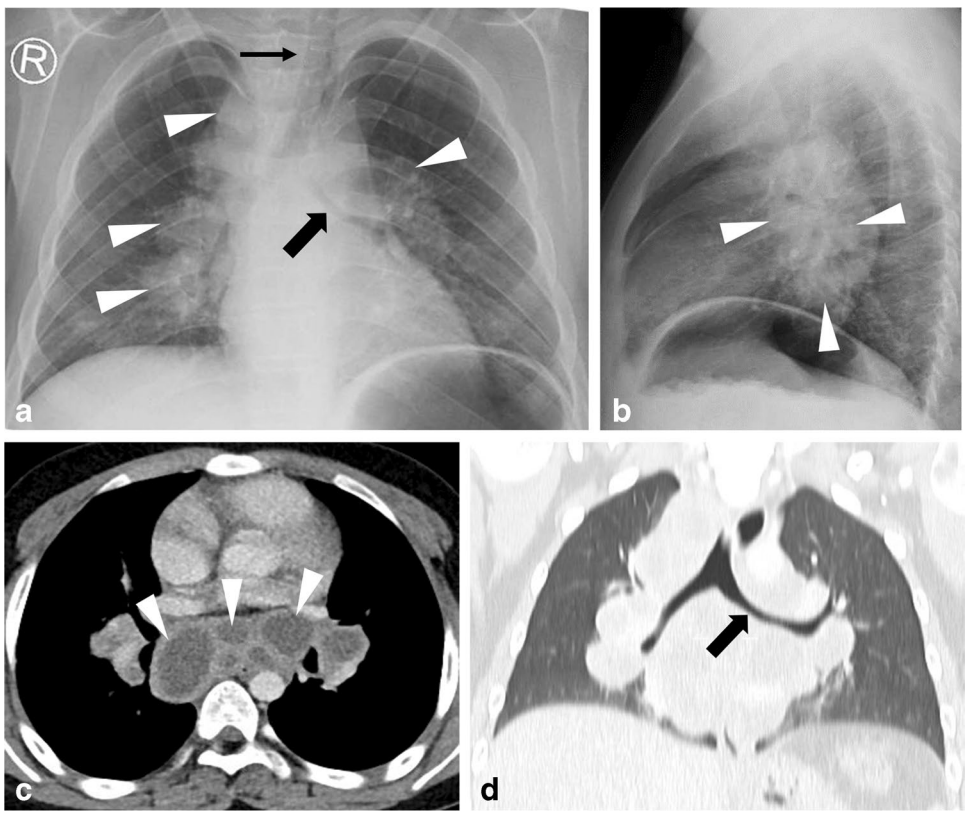

Fig. 1 A 12-year-old boy with severe pulmonary tuberculosis with lymphobronchial involvement. **a**, **b** Posteroanterior (**a**) and lateral (**b**) radiographs of the chest show lobulated soft tissue densities in the hilar and mediastinal regions (*arrowheads*) representing enlarged lymph nodes, with narrowing of the left main bronchus (*thick arrow*) and leftward displacement of the trachea (*thin arrow*). **c**, **d** Contrast enhanced computed tomgraphy scan of the chest. The axial image on soft tissue window setting (**c**) demonstrates the typical central necrosis with a peripheral rim of enhancement in the subcarinal lymph nodes (*arrowheads*). The coronal image on lung window setting (**d**) better delineates the smooth narrowing of the left main bronchus (*arrow*) caused by the enlarged nodes

Mediastinal US, particularly in low-resource settings, may be better than CXR for the detection of enlarged lymph nodes [4, 10, 57], although it is limited by operator dependence [4, 13, 30]. Up to 67% of mediastinal lymphadenopathy was identified on US in children with pulmonary TB who had normal CXR [4, 11, 16, 58]. Interrater agreement was moderate for US (0.56) compared to CXR (0.27) [59, 60] and there was more than 80% agreement between US and CT [11, 58, 59]. Scanning of the mediastinum is performed via a suprasternal approach to visualize the paratracheal and aortopulmonary regions and via an intercostal left parasternal approach to evaluate the subcarinal and prevascular regions [4, 10, 11, 52, 57, 60].

A recent systematic review shows that detection of mediastinal lymphadenopathy with US ranges from 15% to 85%, likely due to differences in study methodology [11, 52, 57, 59]. Although there are no clear criteria for the definition of TB lymphadenopathy [59, 61], there is a statistically significant association of larger lymph nodes with pulmonary TB compared to other respiratory infections [52, 59]. Lymph nodes appear on US as well-defined, ovoid or round hypoechoic structures in comparison to anechoic elongated blood vessels [4, 10, 11, 13, 52], easily confirmed by color Doppler US [10].

Although resolution of tuberculous mediastinal lymphadenopathy is slower than mediastinal non-tuberculous lymphadenopathy, more research is needed to better understand this dynamic [59]. The noninvasive nature of US in the evaluation of mediastinal lymphadenopathy makes this a valuable tool for the follow-up of children undergoing TB treatment [11, 13, 14, 56].

Ultrasound also has significantly higher interrater agreement than CXR for pleural effusion and it can differentiate consolidation from pleural effusion [60]. Although pleural effusion is not diagnostic of pulmonary TB, pleural effusion is more common in children with pulmonary TB [52] and is often associated with consolidation [60].

Computed tomography

CT is a very useful imaging modality in the evaluation of the lungs, mediastinum and chest wall in infants and children. Compared to CXR where there is superimposition of structures, cross-sectional images are best suited to visualize the pattern and extent of parenchymal disease and lymphadenopathy [13, 51, 56]. However, CT may be inaccessible in a low-resource setting where TB is highly prevalent, and entails not only radiation exposure [5, 8, 10, 19], but also intravenous contrast injection and some immobilization. Multi-detector, dual-energy and the emerging photon-counting detector CT technologies are now available not only for better image quality and increasing lesion detection, but also decreasing the radiation dose and sedation rates, which are important advantages especially for infants and young children [51, 62].

CT is the gold standard for the detection of lymphadenopathy and its complications [10, 14, 19, 30, 31, 33, 63, 64] such as airway compression by lymphadenopathy, termed "lymphobronchial TB" (Fig. 1). Presence, pattern (smooth or irregular) and degree of tracheal and bronchial compression causing segmental or lobar collapse or overinflation, bronchiectasis and obstructive pneumonia can be determined by CT [4, 5, 13, 19, 36, 38].

Children with lymphobronchial TB may initially manifest with unremitting cough, stridor and wheezing which may reflect partial airway obstruction. CT can assess this group of patients not only by detecting lymphadenopathy, but also by evaluating and staging associated airway compression and downstream lung parenchymal disease, thereby aiding clinicians to decide the course of treatment [13, 38, 63].

The staging of post-obstructive lung disease differentiates reversible disease from irreversible lung destruction and requires the administration of intravenous contrast. This staging and progression of disease depends on the degree of airway obstruction, whether partial or complete and presence of nodal erosion into the airway lumen. Reversible lung injury is treated conservatively, and includes air trapping, consolidation showing air bronchogram with or without atelectasis and consolidation with fluid bronchogram ("drowned lung") with or without expansile pneumonia. Non-enhancement and cavitation are features of an irreversible and non-salvageable lung which is managed with lobectomy [13, 63].

Pleural effusion can evolve into an exudative effusion or empyema [5, 8] seen on contrast-enhanced CT scan as smooth thickening and enhancement of the visceral and parietal pleura ("split-pleura" sign). An air-fluid level in the pleural cavity may indicate the presence of a bronchopleural fistula. The infected fluid can also extend beyond the parietal pleura to become a subcutaneous abscess, also known as empyema necessitans [5] [Fig. 2].

Magnetic resonance imaging

MRI has emerged as an alternative to CT for imaging children with pulmonary infections and immunocompromised patients [4, 65]. MRI is an imaging modality that has no ionizing radiation, which makes it an attractive alternative. It may be used for diagnosis and follow-up in older cooperative children and patients allergic to iodinated contrast media [66, 67]. Gadolinium-based intravenous contrast media may be administered but are not required [4]. However, MRI has disadvantages; it is less sensitive than CT in the evaluation of the lung parenchyma [51, 68–70], scan times are longer, often necessitating sedation in infants and young children below 6 years old and in patients with claustrophobia and MRI is expensive and not widely available in low-resource settings [4, 14, 19, 51, 63, 71].

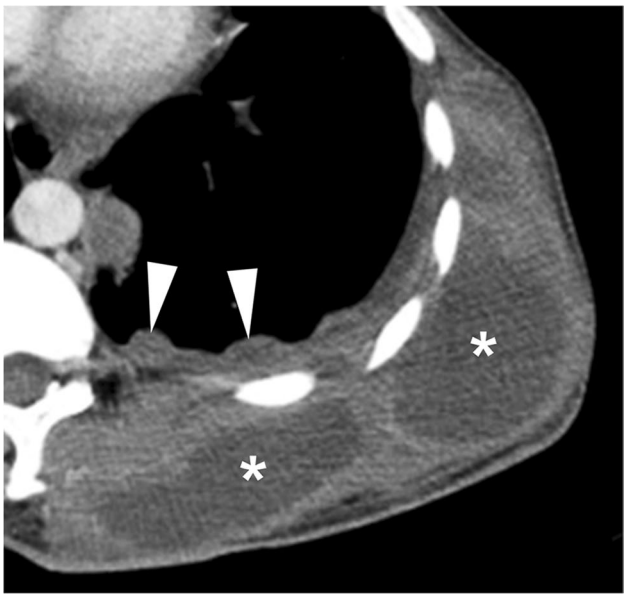

Fig. 2 Contrast-enhanced axial computed tomography image on soft tissue window setting demonstrates subcutaneous abscesses (*asterisks*), also known as empyema necessitans and nodular pleural disease (*arrowheads*) in a 14-year-old boy with complicated thoracic tuberculosis

With technological advances to reduce motion artifact and new protocols for faster acquisition times, MRI of the lung can be used in various clinical applications [4, 7, 51, 70]. MRI is comparable to CT in childhood TB for detecting mediastinal lymph nodes greater than 7 mm in size with sensitivity, specificity and positive and negative predictive values of 100%, as well as in the detection of pulmonary consolidation, nodules greater than 3 mm, presence of cysts or cavities and pleural effusions [14, 56, 66, 70]. MRI is also more sensitive when compared to unenhanced CT for nodal and pleural disease in pulmonary TB [4, 14, 66, 67]. Interobserver agreement ranges from near perfect to perfect in the detection of consolidation, pleural effusion, cyst/cavity, lymph nodes, hyperinflation and bronchiectasis [4]. However, ground glass opacities, small nodules and calcified nodules may be missed [56, 71].

Another advantage of MRI is that it can determine disease activity within the infected nodes by the presence of restricted diffusion and post-contrast enhancement [4, 13, 14]. MRI can differentiate TB lymphadenopathy from reactive lymph nodes using short tau inversion recovery/T2-weighted sequences which can demonstrate the characteristic low signal in TB [13, 14] due to the presence of paramagnetic free radicals secreted from active phagocytic cells [72]. In contrast, central hyperintensity indicates liquefactive necrosis [4, 19, 73].

For pleural effusion or empyema, MRI is as sensitive and specific as CT, and according to Sodhi and colleagues, MRI is better than CT in demonstrating septations and internal

Table 1 Clinical condition and recommended imaging modalities for children suspected to have pulmonary tuberculosis (TB)

Imaging recommendations	References	Comments
Chest radiography remains an important imaging tool for diagnosis of children with suspected pulmonary TB	4, 5, 9–12, 15–19	Findings are nonspecific with poor accuracy and wide intra- and interobserver variability
Mediastinal ultrasound, when available, is in low-resource settings the initial and follow-up imaging modality for detecting adenopathy in childhood TB	4, 5, 9, 58, 59	Value is limited by operator dependence
Computed tomography (CT) with intravenous (IV) contrast is the modality of choice for detection and staging of complications, particularly lymphobronchial TB	4, 10, 19, 32, 34, 38, 64, 65	CT staging can also determine the course of treatment
Magnetic resonance imaging is an appropriate alternative to CT, when available, for patients suspected to have lymphobronchial TB	4, 64, 69, 73, 74	1. IV contrast is not required 2. For patients not requiring sedation (i.e. > 6 years of age, cooperative or without claustrophobia, patients with allergy to iodinated contrast)

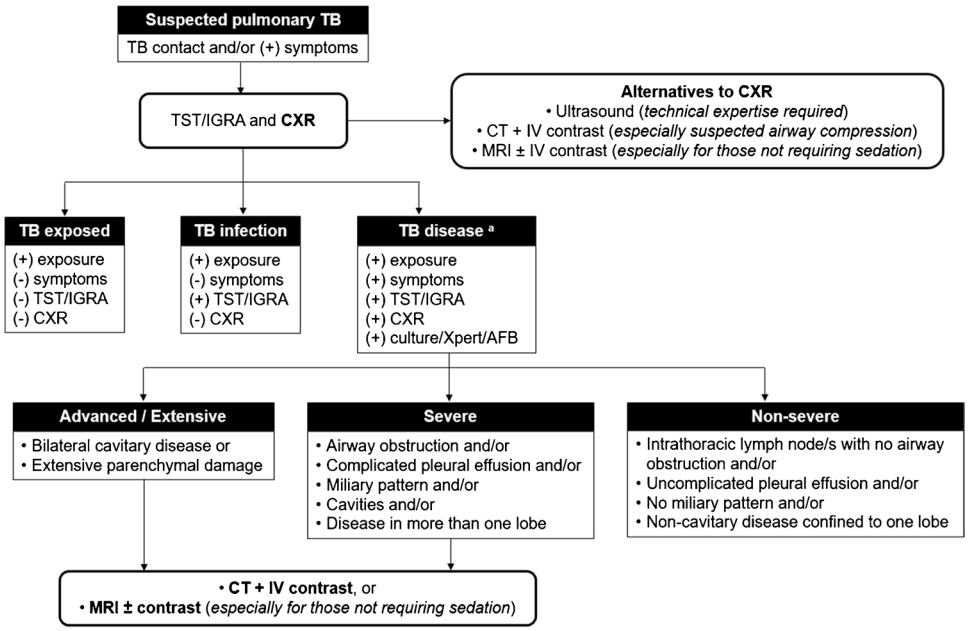

Fig. 3 Evidence-based algorithm for the imaging of children with suspected pulmonary tuberculosis (TB). [a] not all criteria are present in all cases. In certain cases of TB disease: (1) history of TB exposure may be difficult to establish. (2) There may be false negative TST/IGRA. (3) There may be false negative CXR. (4) There may be false negative culture/Xpert/AFB due to the paucibacillary nature of TB in children. *AFB* acid-fast bacilli, *CT* computed tomography, *CXR* chest X-ray, *IGRA* interferon-gamma release assay, *IV* intravenous, *MRI* magnetic resonance imaging, *TST* tuberculin skin test, *US* ultrasound, (+) positive or present, (-) negative or absent

debris as well as paraspinal soft tissue and chest wall muscle involvement [66, 74]. Diffusion restriction of the fluid collection may help differentiate empyema and abscess from transudative pleural effusion.

MRI, unlike CT, can differentiate caseating TB consolidation from non-caseating consolidation secondary to other causes. The former characteristically has low T2 signal intensity [4, 14, 56, 63, 73], while the latter has high T2 signal intensity [63].

To minimize radiation exposure, MRI is appropriate in the follow-up of nodal and parenchymal disease in children with thoracic TB [4].

Positron emission tomography

Positron emission tomography (PET) is commonly used in the imaging of cancers but less utilized for infectious diseases. PET using ^{18}F-fluorodeoxyglucose (FDG) is said to be highly sensitive for detecting tuberculous lesions [75–78]. FDG-PET/CT scan also assesses disease activity and monitors response to therapy. Active tuberculomas are FDG-avid (maximum standardised uptake value [SUV_{max}]> 2.5) while inactive disease has an $SUV_{max} < 1.5$) [78]. However, differentiation between oncological, inflammatory and infectious processes is challenging [77]. The lymphadenopathy of active TB is also FDG-avid but is difficult to distinguish from other causes of lymphadenopathy, such as lymphoma [78]. Pathogen-specific imaging approaches using compounds such as radioanalogues of para-aminobenzoic acid [77, 79] and trehalose [77, 80] are still in the early stages of development but in the future could improve the sensitivity of PET. Further studies are recommended to assess the potential role of PET in the diagnosis of thoracic TB in children.

The recommended imaging modalities and algorithm for children with suspected pulmonary TB are summarized in Table 1 and Fig. 3, respectively.

Conclusion

Tuberculosis primarily affects the lungs and lymph nodes but can have a diverse spectrum of thoracic manifestations and complications. Medical imaging, along with clinical data and laboratory examinations, plays a crucial role in the diagnosis, characterization and documentation of the extent of the affected structures and in the evaluation of complications in children suspected of having TB. Knowledge of the appropriate imaging tool for a specific clinical indication is important. This will depend on the severity of the patient's condition, age, availability of imaging resources and expertise of the interpreting radiologist or physician. Imaging recommendations and algorithms are presented in this article which are intended to help guide both radiologists and clinicians in making timely and accurate medical decisions.

Author contribution B.F.L., N.D.P.C., S.A., Z.A.M., M.I.M.A. and K.S.S. conceived the project, searched and collected relevant articles from the literature. N.D.P.C. acquired and interpreted the images, and drafted the initial manuscript. All authors reviewed, edited, proof-read and approved the final manuscript.

Declarations

Conflicts of interest None

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